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Review Article:

Exploring the Regulatory Role of Long Non-Coding RNA in Breast Cancer: A Review of Current Insights

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Abstract

Context: The cancer epidemic is getting worse every day. Breast cancer is one of the leading causes of mortality worldwide, including in Pakistan. This condition is progressing due to a number of variables. According to recent investigations, lncRNAs play a major role in cancer development.

Evidence Acquisition: The post-surgical breast tissue samples were acquired by contacting different hospitals. The analysis of lncRNA expression profiles of publicly available breast cancer datasets will be done using overlapping Bioinformatics tools. To support the suggested mechanisms of lncRNA regulation in breast cancer, the experimental data will be compared.

Results: Almost 1900 lncRNA gene annotated in human genome so far (Gencode 41), which is almost equal to the number of genes that code for proteins. The effective characterization of lncRNAs remains a significant challenge in molecular biology, prompting numerous high-throughput initiatives and is a critical scientific priority. The great clinical potential that these molecules hold has sparked lncRNA research, which has been founded on the characterization of their expression and functional mechanisms.

Conclusion: This review depicted lncRNA role in breast cancer. Protein-coding genes and lncRNA are related to the development of breast cancer.

Keywords: LncRNAs, Breast Cancer, gene expression, cancer biology, functional mechanism, molecular biology.

1. Context

According to data from the World Health Organization (WHO), breast cancer is the most common malignancy among women globally. It ranks as a leading cause of mortality in low-income countries and is the second leading cause of cancer-related deaths among women in the United States [1]. However, the differences in mortality rates are less pronounced. Breast cancer is a highly dynamic disease, influenced by both environmental and genetic factors. It exhibits considerable variation at

both genomic and clinical levels. Each subtype displays distinct biological traits, pathological abnormalities, and clinical outcomes, all of which affect treatment strategies. Molecular and environmental data, along with structural markers, are essential for classifying breast carcinomas into subtypes. Historically, breast cancers were categorized based on distinct molecular signatures, including Progesterone Receptor (PR), Estrogen Receptor (ER), and Human Epidermal Growth Factor Receptor 2 (HER2), using conventional immunohistochemistry assays [2].

Cancer is a disease that arises when the normal cell growth cycle is disturbed, resulting in the formation of an aberrant and abnormal mass of cells [3]. Metastasis is the process by which the aberrant mass of cells spreads to other areas of the body via the bloodstream, departing from the initial site of development. Cancer stem cells are significant in controlling the abnormal cell masses and their subsequent metastases to other bodily areas [4]. In Pakistan, nearly 100,000 new cases of breast cancer are diagnosed each year, making it the most common type of cancer in the country. It accounts for 40,000 to 45000 annual fatalities according to a 2024 report. These figures suggest that approximately 38.5% of all cancer-related fatalities in Pakistan were caused by breast cancer [5]. The majority of women in Pakistan, a developing nation, have very limited access to health care services due to illiteracy, inadequate healthcare facilities, and gender-based disparities. Based on certain immuno-markers found on their cell surface, breast cancer is classified into four kinds. In reality, these markers are receptors, and the classification depends on their presence or absence.

Transcriptional profiling of a wide range of tumors has led to further classification, revealing five main genetic subtypes. Breast carcinomas typically originate from luminal or basal cells within the ductal or lobular units of the mammary glands [6]. These malignancy subtypes represent unique biological entities associated with specific cell types, with their gene expression profiles reflecting the biological complexity of the disease. Classifying patients based on these molecular subtypes results in varied medical outcomes and responses to therapy. Luminal tumors, which are predominantly ER-positive, exhibit slower growth but have a higher risk of relapse. These tumors are treated with a combination of chemotherapy and endocrine therapy to reduce hormonal receptor upregulation. The HER2-positive subtype is characterized by the overexpression of the HER2 gene and an unfavorable prognosis [7]. Treatment for this subtype typically includes chemotherapy along with targeted therapies aimed at HER2. The basal-like subtype, commonly found in triple-negative breast cancers, is one of the most invasive variants and has the worst prognosis for patients. However, when detected at early stages, it can be treated in approximately 80% of cases [8].

Among all mammalian species, the breasts are very distinct mammary glands. It is mostly made up of ducts and lobules. Milk is produced by lobules and drained to the nipple areola for milk ejection via lactiferous ducts. The anatomy of the breast also includes a network of lymph nodes, blood vessels, lymph vessels, and nerves. Anatomically, the breast consists of two major components: the stromal and the glandular sections [9]. The stromal section essentially consists of the tissues, such as muscles, lipids, and fascia that support the breast's function, while the glandular regions aid in the production of milk. Breast cancer begins as a tumor, mass of cells, which becomes malignant when it gains the ability to spread to other areas of the body. EMT plays a critical role in metastasis [10]. The epithelial to mesenchymal lays the foundation for cell to break off from one another and travel to various physically areas. Tumor stem cell extravasation is made possible by the circulatory and lymphatic systems. The combination of genetic and epigenetic adjustments, in combination with aberrant interlinking in the microenvironment that transforms breast epithelial cells, constitute the basis for metastatic breast cancer. Researchers to cancer cells that exhibit stem cell-like characteristics have attributed the origin, creation, and recurrence of breast cancer [11-12]. While most sequences are transcribed under specific conditions, it has been discovered that only a small fraction of these transcripts actually produces proteins [13]. The predominant transcript group, long non-coding RNAs (lncRNAs), has emerged as a key regulator of gene expression. Increasing evidence suggests that the deregulation of lncRNA loci can disrupt the normal transcriptional landscape, leading to abnormal gene activity and, ultimately, cancer. A comprehensive characterization of these newly discovered RNA molecules could offer valuable insights into novel treatment approaches and therapeutic strategies [14]. The unique characteristics of lncRNAs, including their gene expression patterns and multifunctional tertiary structures, make them promising as diagnostic biomarkers and potential targets for pharmacological interventions [15].

Several criteria are taken into consideration when

diagnosing breast cancer. To check for the presence of any lumps, the breasts are first physically palpated. Ultrasound and mammography provide images of the size and location of lumps. In order to accurately determine the stage and grade of the tumor, a biopsy is finally obtained, stained, and examined under a microscope [16]. RNAs without coding potential are known as long noncoding RNAs, or LncRNAs. They do not convert into molecules of proteins. They play a role in posttranscriptional control, transcription, translation, and other activities. They serve as activators to aid in the folding of proteins [17]. Additionally, lncRNA is essential for cell invasion, proliferation, apoptosis, and metastasis. Numerous biological and pathological processes are regulated by lncRNAs. By altering specific signaling pathways, both the upregulation and downregulation of lncRNAs are significantly implicated in tumor development. If not diagnosed and treated early, tumors can metastasize to other organs [18]. One of the numerous risk factors for breast cancer is a mutation in the BRCA1 or BRCA2 gene [19]. Compared to men, breast cancer is more common in women and is linked to a high death rate. This is more common in western nations. LncRNAs influence both the initiation and suppression of BC. LncRNA can act as either promoters and inhibitors of breast cancer invasion and metastasis [20].

2. Evidence Acquisition

LncRNAs roles in the nucleus

Since a significant portion of lncRNAs are expressed nearly exclusively in the nucleus, they have roles in nuclear activities including organizing functionally different nuclear domains or controlling RNA transcription and splicing. Various processes affect the nuclear localization of lncRNAs. Depending on whether they affect local genes or long-distance domains, lncRNAs can be classified as either cis- or trans-acting. This is because their nuclear functions usually align with the regulation of gene expression. Since the precise nucleotide pattern of lncRNAs may or may not determine their function, their action can also be classified as either sequence-dependent or independent [21].

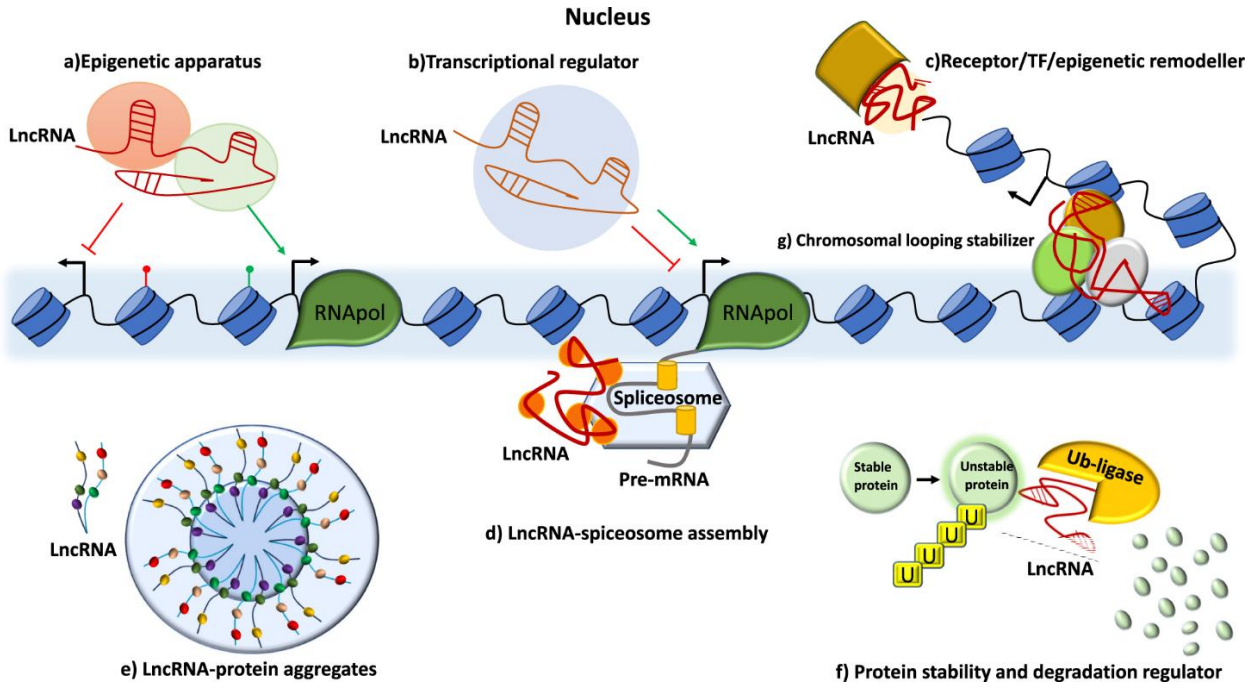


Figure 1. Schematic representation of lncRNA mechanism in nucleus [22]

LncRNAs as Chromatin Status Regulators

Regulation of chromatin state is a recurring theme in nuclear functions. Long non-coding RNAs (lncRNAs) have been shown to exert multiple effects on chromatin structure. In cis-acting mechanisms, lncRNAs modulate chromatin at their site of

transcription, influencing the expression of nearby protein-coding genes, as shown by sequencing data [23].

HOTAIR

HOX transcript antisense intergenic RNA (HOTAIR), an well-known instance of a nuclear lncRNA that acts both as a scaffold and a biological guide, is one of the most notable lncRNAs related to cancer [24]. The conserved protein-coding genes known as HOX genes are arranged in several genome clusters and are involved in the regulation of proper body patterning. HOX genes are often overexpressed in cancer and are strictly controlled during development [25]. lncRNA The 2.1 kb conserved transcript known as HOTAIR is continuously polyadenylated and translated [26]. It is composed of six exons and originates from the HOXC region on chromosome twelve. First, it has been proposed that the distal HOXD cluster corresponds to where HOTAIR modulates Tran's chromatin. In fact, the locus is de-repressed and the repressive histone modification H3K27me3 is decreased when HOTAIR is knocked down by siRNAs [27]. In many cancer types, this lncRNA is commonly observed to be dysregulated [mainly over-expressed]. According to reports, HOTAIR abnormally targets genomic areas other than the HOXD cluster in relation to breast cancer, causing chromatin dysregulation and encouraging the spread of breast tumors [28].

Functions like Enhancers

Enhancers are areas of open chromatin that serve as a medium for various transcriptional binding sites and work differently depending on the type of cell to increase the expression of target genes [29]. Enhancers work by cis-acting on neighboring genes, which can even be located several kb away because long-range chromatin connections are formed. Enhancers that are actively transcribed also produce noncoding transcripts, which can be longer and processed more frequently or short and quickly broken down (eRNAs). Through a variety of methods, these non-coding RNAs may contribute to an enhanced function [30]. Here, we outline the documented enhancer-like actions of two lncRNAs implicated in breast cancer.

A-ROD

In certain cases, enhanced regulatory functions may be directly influenced by the processed [mature] forms of long non-coding RNAs (lncRNAs), rather than by their original unprocessed transcripts. Dickkopf-1 (DKK1) acts as a negative regulator of the Wnt signaling pathway and is modulated by the lncRNA A-ROD [31]. A-ROD is a non-coding transcript derived from an enhancer locus located approximately 130 kb upstream of the DKK1 locus [32]. These two loci have been found to be co-expressed and physically linked through chromatin looping in both patient samples and breast cancer cell lines (e.g., MCF-7). Interestingly, small interfering RNAs (siRNAs) targeting the mature A-ROD transcript significantly reduced DKK1 expression and increased RNA polymerase II pausing at the DKK1 transcription start site [33]. In contrast, antisense oligonucleotides (ASOs) directed at the nascent A-ROD transcript had no effect on DKK1 mRNA levels. This suggests that A-ROD is not involved in establishing chromatin looping, unlike lncRNAs such as CCAT1-L [34].

Instead, the mature A-ROD transcript recruits the transcriptional activator EBP4, which enhances DKK1 expression, with the pre-existing chromatin configuration maintaining close spatial proximity between the A-ROD and DKK1 loci. Experimental data on splicing inhibition and transcriptional termination further support the conclusion that the mature A-ROD transcript mediates its enhancer-like function [33]. The weak chromatin association of the mature lncRNA, combined with its transcription from regions involved in chromatin looping, suggests that it functions as a modulator of gene expression. This is further supported by bioinformatics studies showing a correlation between enhancer activity and the transcription and splicing of the lncRNAs they encode.

CCAT1-L

The long isoform of the lncRNA gene colon-cancer-associated transcript 1 (CCAT1-L) was named for its elevated expression in colorectal cancer (CRC) tissue. The 5.2 kb CCAT1-L RNA is associated with chromatin and is transcribed from a site exhibiting increased enrichment. It is located on chromosome 8q24, approximately 500 kb upstream of the MYC locus [35-36]. Three-dimensional chromosome conformation capture data have revealed molecular connectivity between MYC-515, MYC-335, and the MYC promoter. Notably, MYC expression and the frequency of interactions among MYC, MYC-335, and MYC-515 decrease when CCAT1-L is downregulated by antisense oligonucleotides (ASOs) [37]. These findings underscore the essential role of the CCAT1-L transcript in modulating enhancer activity beyond the intrinsic DNA features at the transcriptional locus. The proposed model suggests that CCAT1-L acts in cis, facilitating long-range chromatin

interactions that bring the MYC locus into proximity with its enhancers through direct interaction with the CCCTC-binding factor (CTCF) [38]. Given the broad oncogenic influence of MYC, it is not surprising that CCAT1-L is frequently overexpressed in various cancer types. Regardless of receptor status, CCAT1-L expression serves as a promising prognostic biomarker in breast cancer [39], correlating with reduced overall and progression-free survival [40-41].

Table 1. Key Long Non-Coding RNAs [lncRNAs] Mechanism of Action, Biological Role and Associated Diseases [42-43].

lncRNA	Mechanism of Action	Biological Role	Associated Diseases
XIST	X chromosome inactivation by coating and silencing one X chromosome in females	Dosage compensation, epigenetic regulation	X-linked disorders, cancers
HOTAIR	Scaffold for PRC2 (Polycomb Repressive Complex 2) and LSD1 to modify chromatin	Epigenetic silencing of tumor suppressor genes	Breast cancer, other malignancies
MALAT1	Binds splicing factors and regulates alternative splicing	mRNA processing, cell cycle regulation	Metastasis, lung cancer, neurodegeneration
NEAT1	Forms nuclear paraspeckles to sequester proteins and RNAs	Stress response, viral defense, nuclear organization	Neurodegenerative diseases, cancers
ANRIL	Recruits PRC1/PRC2 to silence tumor suppressor genes (e.g., CDKN2A/B)	Cell proliferation, senescence regulation	Cardiovascular disease, cancer
TUG1	Interacts with PRC2 and regulates gene expression	Retinal development, cell growth control	Diabetic retinopathy, cancers
GAS5	Acts as a decoy for glucocorticoid receptor (GR), inhibiting its activity	Apoptosis, growth suppression	Breast cancer, autoimmune diseases
LINC-PINT	Binds to PRC2 and suppresses oncogenic transcription	Tumor suppression, cell cycle arrest	Glioblastoma, other cancers
PVT1	Sponges miRNAs (e.g., miR-200 family) and stabilizes MYC oncogene	Cell proliferation, apoptosis resistance	Multiple cancers
H19	Acts as a miRNA sponge (e.g., for let-7) and regulates imprinting	Embryonic development, growth control	Beckwith-Wiedemann syndrome, cancers

Control of Splicing

It has recently been demonstrated that lncRNAs utilize an additional way of controlling gene expression by modulating gene splicing. Several isoforms that are regulated differently in physiology and disease can be influenced by the use of alternative splice sites [44]. Splicing is a crucial stage of mRNA maturation that makes it possible to separate introns from transcripts [45]. Under hypoxia and DNA damage, c-JUN and other survival genes produce the lncRNA linked to SART3 control of splicing (LASTR), a stress-related symptom [46]. This portrayal is remarkable. Because c-JUN is often overexpressed in epithelium malignancies, The Cancer Genome Atlas TCGA showed that LASTR was significantly expressed across the majority of breast cancer subtypes. According to RNA pulldown studies followed by mass spectrometry, this 714 nt

lncRNA, which is made up of two exons produced primarily in the nucleus, interacts with SART3, a splicing protein that aids in the formation of the U4/U6 ribonucleic complex [47]. ASO-based knockdown experiments suggest that LASTR has a beneficial impact on splicing regulation worldwide. By inhibiting spliceosome subunit recycling and reducing SART3 disassembly from the U4 snRNA, this enhances intron continuation, exon skipping, and non-sense-mediated mRNA breakdown [48]. Under stress, normal mammary epithelial cells produce LASTR in response to hypoxia, which helps SART3 dissociate from the U4/U6 snRNP and preserves cell function [49]. By avoiding splicing errors, the foundation overexpression of LASTR also aids in the fitness of cancer cells [50]. Surprisingly, LASTR inhibition can slow the growth of cancers in animal xenografts and increase the radiation sensitivity of the triple-negative breast cancer cell line MDA-MB-231, indicating that this lncRNA may be a viable target for immunotherapy [51]. This study demonstrates that a single lncRNAs dynamic control can have a major impact on fundamental biological cellular functions and how cancer cells might profit from these straightforward but successful strategies.

Nuclear Architecture Organization

Some lncRNAs that are considerably expressed in the nucleus may coordinate the activity and structure of completely distinct nuclear compartment [52]. These lncRNAs appear in different compartments after being transcriptionally induced from proximal loci. The formation of paraspeckles, a dynamic compartment in charge of transcription and RNA processing, depends on the localized protein NEAT1 [53]. NEAT1 has been associated with actively transcribed genes. NEAT1's sequence contains multiple protein-interacting domains that enable it to accurately target proteins within this compartment. NEAT1 communication [54], which is aberrant in numerous cancer types, can be detected in the peripheral blood of individuals with breast cancer. Increased NEAT1 expression correlates with poor prognosis and reduced overall survival. The expression of NEAT1, which regulates genes involved in invasion, metastasis, and chemoresistance, is influenced by various tumorigenic transcription factors, including NFkB and STAT3. Nuclear speckles, sub-nuclear regions where spliceosome components aggregate, encompass the conserved lncRNA MALAT1 [55]. MALAT1 aids in pre-mRNA splicing, according to this present paradigm. The concept states that MALAT1 knockdown modifies the structure and activity of nuclear speckles without altering cell proliferation [56]. The reduction in phosphorylation levels of serine/arginine-rich proteins, which are critical splicing components, may account for the impact of MALAT1 silencing on splicing. MALAT1 overexpression is often linked to metastasis, unfavorable prognosis, and challenges in radiation and chemotherapy across various human malignancies, including breast cancer. Tandem duplications of the MALAT1 gene have been documented. Nevertheless, MALAT1 inhibits primary growths in breasts and breast cancer cells. Based to this work, MALAT1 inhibits the expression of pro-metastatic target genes and communicates between it and the YAP co-activator by communicating with TEAD. When interpreting a complicated and frequently employed lncRNA such as MALAT1, these distinct points of view may coexist instead of be mutually exclusive [57].

LncRNAs' roles in the cytoplasm

A significant amount of lncRNAs is capable of carrying out their intended roles in the cytoplasm after having been released from the nucleus. Many lncRNAs are long, A/U-rich transcripts with few exons that depend on the NXF1 factor for export, per a relatively recent study [58]. Once there, lncRNAs can attach to proteins or nucleic acids or be separated into different organelles like exosomes or mitochondria. Another example is the nuclear-encoded lncRNA SAMMSON, which has been re-located into mitochondria and produced in melanoma cells. It performs an important role in controlling mitochondrial metabolism by connecting to p32. As with several lncRNA cytosolic functions, the sorting among various cellular compartments is still unclear However, it is widely acknowledged that it depends on the way lncRNAs interact with other RNA species and/or RNA-binding proteins (RBPs) [59]. The crucial stoichiometric ratio between lncRNA and its target molecule is the most important indicator of lncRNA/target interaction hat could be potentially an RNA or protein molecule. In reality, cis-acting lncRNAs only require a few copies for significant effects on a single target gene in the neighborhood [60]. Like other cytoplasmic lncRNAs, trans-acting lncRNAs must first undergo a thorough copy number analysis of both the target and the lncRNA to determine the plausibility of the suggested biological mechanism [61]. This has a special impact on lncRNAs that act as competitive endogenous RNAs [ceRNAs] [16, 62]. lncRNA expression may be restricted to specific cell types, such as rare stem cells, or associated with particular tissues, distinguishing between normal and malignant forms [63]. Consequently, instead of

employing a bulk population that may encompass various cell types, a comprehensive stoichiometric assessment accounting for sample purity should be utilized to elucidate the biological effects mediated by the lncRNA.

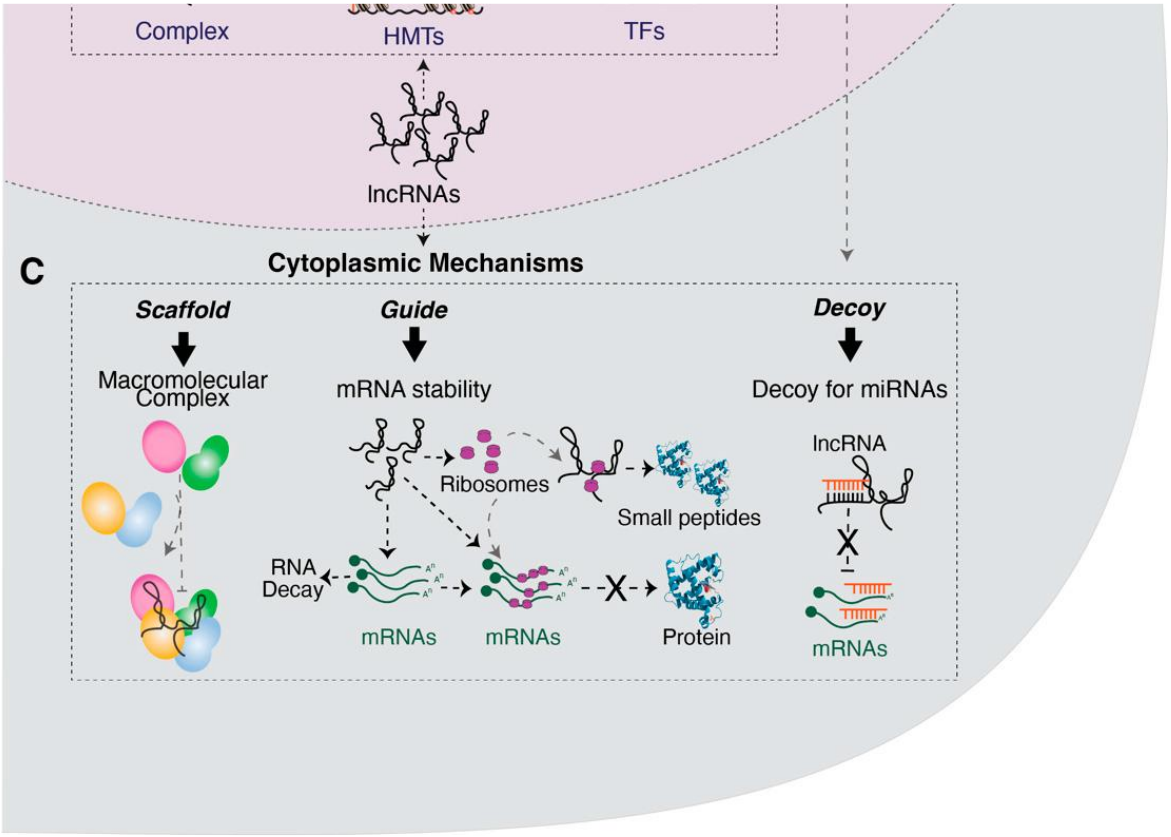


Figure 2: Genomic activity and molecular functions of lncRNA [25]

LncRNAs Functioning as Sponges for miRNA

The competitive endogenous RNA (ceRNA) responsible for hESC self-renewal was first identified as LncRNA-regulator of reprogramming, or Linc-ROR. Subsequent to an elevation in hESC, linc-ROR levels diminish during differentiation [64]. The Linc-ROR sequence's microRNA responsive elements (MREs) had to match miR-145 in order for the ceRNA activity to occur [65-66]. A study utilizing the normal breast epithelial cell line MCF10A offered early insights, identifying Linc-ROR as a competing endogenous RNA (ceRNA) that can elevate ZEB2 levels, a transcription factor that promotes epithelial-mesenchymal transition (EMT) and is a recognized target of miR-205, and sponge miR-205 [67]. In addition to explaining the impact of Linc-ROR development on cell movement, development, and the development of specific characteristics, such as the increased CD44high/CD24low population and the capacity to form no adherent spheroids (mammosphere), this procedure also explains the rise in mesenchymal marker expression [68]. A recent study on MCF7 cells revealed that Linc-ROR functions as a competing endogenous RNA for miR-194-3, enhancing MECP2 levels, which promotes invasion, proliferation, and resistance to rapamycin in breast cancer cells. For lign-ROR, a further mechanism promoting the formation of ER+ tumors in breasts that are resilient to tamoxifen and not dependent on estrogen was also described. The proposed mechanism states that MAPK/ERK signaling becomes active as a result of direct suppression of the phosphatase DUSP7 [69]. This causes the estrogen receptor to become phosphorylated in which promotes the proliferation of breast cancer cells and improves their resistance to hormonal therapy.

H19

The written record from the H19 locus was amongst the earliest lncRNAs to be discovered. The IGF2 locus is epigenetically silenced by a repetitive imprinted locus on human chromosome 11 that

encodes a cytosolic transcript measuring 2.3 kb in length [70]. Furthermore, H19 has been identified as a precursor for miR-675 in mouse embryonic and extra-embryonic cell lines. It may regulate IGF2 abundance on two levels by imprinting the gene locus and blocking the IGF1R receptor with miR-675 [71], thereby affecting placental development [72]. Increased tumor growth aggressiveness, metastasis in vivo, and proliferation have been all linked to increased H19/miR-675 expression in breast cancer cells. Mechanistic [73]. According to the hypothesis, this is dependent on the activity of miR-675 in b-Cbl and c-Cbl mRNAs, which hyper activates EGFR and c-Met and thereby starts Akt and Erk signalling [74]. A prototype ceRNA mechanism that is active during muscle development is also highlighted by the description of H19 as a miRNA sponge for Let-7. A number of investigations have demonstrated that the ceRNA pathway additionally exists in breast tumors. For example, it has been demonstrated that by regulating WNT signaling, the interaction between H19 and Let-7c influences whether cancer stem cells (CSC) divide symmetrically or asymmetrically. The pluripotency factor and a transcription factor necessary for stem cell production, Let-7a/b and LIN28, were found to interact with H19 in a separate study [17]. According to a positive feedback theory, competition between H19 and LIN28 for Let-7a/b binding raises LIN28 levels. As a result, not all of the Let-7 miRNA target genes are depressed since mature Let-7a/b molecules can be produced from precursors [75]. Finally, H19 has been shown to release HIF1 mRNA levels and sequester Let-7 miRNAs under hypoxic conditions. This study showed that the H19/Let-7/HIF-1 axis acts as a gatekeeper for metabolic processes by regulating the transition from OXPHOS to glycolysis in hypoxic environments [18].

Using LncRNAs as a Guide

NORAD

By functioning as a regulator of mRNA translation or devastation, lncRNAs in the cytosol may regulate mRNA stability in in addition to functioning as miRNA sponges. One excellent example is the non-coding RNA triggered by DNA damage (NORAD) [76]. The cytoplasm includes tremendous quantities of this lncRNA that functions as a decoy by binding to PUMILIO1/2 proteins. This process requires the NORAD, a specific order that includes multiple PUMILIO response elements (PRE), an 8 NT segment that typically occurs in the 30 UTR of PUMILIO designated mRNAs. NORAD maintains chromosomal integrity and serves as a reservoir for PUMILIO1/2 proteins during genotoxic stress [77]. Chromosomal instability is induced by the aberrant synthesis of PUMILIO1/2 proteins, which associate with and accelerate the mRNA degradation of essential targets for DNA repair and replication upon the removal or downregulation of NORAD [78]. Replication fork speed is slowed down as well, chromosomal segregation challenges increase, and the cell cycle has been altered in NORAD-depleted cells [79]. It has been proposed that NORAD suppresses breast cancer tumors. The usually carcinogenic YAP/TAZ and NuRD complexes have been shown to transcriptionally suppress NORAD. Further, it has been determined that NORAD operates as a decoy for S100P, preventing its pro-migratory and pro-invasive conduct [80].

Polypeptides Encoding LncRNAs

Their definition states that lncRNAs should not be able to code. However, some research revealed that tiny polypeptides can participate in lncRNA-regulatory roles and synthesized small open-reading frames (ORFs). For example, it has been demonstrated that LINC00665 encodes a 5.5 kDa micro peptide called CIP2A-BP in breast cells [81]. This micro peptide binds to CIP2A and competes with the oncogene PP2A, which promotes the growth of tumors. The finding that the TGF and SMAD pathways regulate LINC00665 translation but have no effect on overall levels is noteworthy [82]. According to this model, The overexpression of the CIP2A-BP protein, in contrast to LINC00665 expression, can suppress the migratory and invasive characteristics of triple-negative breast cancer cells in both in vitro and in vivo environments [6, 83]. One common lncRNA discovered in breast epithelial tissue is EPR [epithelial cell program regulator], whose expression is suppressed by TGF. It has been demonstrated that the ~8 kDa short peptide that LncRNA EPR encodes localizes in the mammary gland epithelial cell junctions along with junctional proteins like ZO-1, CGNL1, and Contactin [84]. It was proposed that lncRNA EPR had two mechanisms. It can interact with the chromatin-bound Cdkn1a gene and maintain the stability and production of Cdkn1a mRNA at the RNA level, which promotes cell cycle arrest and epithelial phenotype [85-86].

PVT1: Multiple Functions, One lncRNA

Numerous long non-coding RNAs [lncRNAs] perform diverse regulatory functions, often associated with complex and sometimes contradictory phenotypes. Plasmacytoma variant translocation 1 (PVT1) is a notable example of such a multifunctional lncRNA [69]. The genomes of

mice and rats display significant similarity to the human PVT1 gene. Expression of PVT1 lncRNA is regulated by six distinct transcription start sites (TSS), spread across a 300 kb region downstream of the MYC oncogene promoter. The 8q24 chromosomal region, which encompasses both MYC and PVT1, is frequently mutated in cancer. In particular, amplifications and structural alterations at this locus often result in the co-amplification of these two genes [87-89] have been identified within the PVT1 locus and may function as oncomiRs by promoting cell proliferation, reducing stress-induced apoptosis, and enhancing glycolytic metabolism. However, other studies have shown that these same miRNAs can also exert tumor-suppressive effects, suggesting that their impact is likely tissue-specific, and dependent on cellular context [90].

Additionally, the PVT1 sequence contains multiple miRNA response elements (MREs), indicating that the transcript may act as a molecular sponge [91]. Several studies support the idea that PVT1 sequesters tumor-suppressive miRNAs, thereby activating pro-survival and proliferative pathways and contributing to metastatic progression [92-93].

Table 2. Functional and clinical significance of lncRNAs in Breast Cancer [94-97].

lncRNA	Expression in Breast Cancer	Mechanism of Action	Biological Function	Clinical Implications
HOTAIR	Upregulated	Binds PRC2 & LSD1 to silence tumor suppressors (e.g., **PTEN, BRCA1**)	Promotes EMT, metastasis, and therapy resistance	Poor prognosis, chemoresistance
MALAT1	Upregulated	Regulates splicing(e.g., **B-MYB, SF2/ASF)** and promotes angiogenesis	Enhances proliferation, invasion, and metastasis	Associated with TNBC and poor survival
GAS5	Downregulated	Sponges miR-21, inhibits GR signaling, upregulates p53	Induces apoptosis, suppresses growth	Tumor suppressor, potential therapeutic target
XIST	Downregulated [loss in some subtypes]	Mediates X-chromosome inactivation; loss leads to oncogene activation	Modulates hormone receptor signaling (ER/PR)	Linked to hormone resistance
NEAT1	Upregulated	Forms paraspeckles, stabilizes **HIF-1α**, sponges miR-448	Promotes hypoxia adaptation and stemness	Correlates with advanced stages
ANRIL	Upregulated	Recruits PRC1/PRC2 to silence **CDKN2A/B (p16/p15)**	Drives cell cycle progression, anti-apoptosis	Poor prognosis in ER+ cancers
H19	Upregulated	Sponges **let-7**, activates **IGF2**, promotes EMT via **miR-200b/c**	Enhances proliferation, stemness, and metastasis	Biomarker for aggressive subtypes
PVT1	Upregulated	Stabilizes **MYC**, sponges **miR-200 family**	Suppresses apoptosis, promotes chemo-resistance	Associated with TNBC and relapse

LINC00511	Upregulated	Binds **EZH2**, silences **LATS2** (Hippo pathway)	Promotes proliferation and invasion	Poor survival in luminal B tumors
BCAR4	Upregulated	Activates **GLI2** (Hedgehog pathway) via SNIP1/PNRC1	Drives tamoxifen resistance	Predicts endocrine therapy failure
LINC00673	Upregulated	Sponges **miR-515-5p**, activates **MARK4/ERK** pathway	Enhances migration and invasion	Linked to lymph node metastasis
DANCR	Upregulated	Binds **CTNNB1** (β-catenin), activates Wnt/β-catenin	Promotes stemness and EMT	Correlates with recurrence
MEG3	Downregulated	Binds **p53**, inhibits **MDM2**, suppresses **VEGF**	Induces apoptosis, anti-angiogenic	Tumor suppressor, lost in aggressive tumors
UCA1	Upregulated	Sponges **miR-143**, upregulates **HER2**, activates **AKT/mTOR**	Promotes growth and chemo-resistance	Associated with HER2+ tumors
LINC00963	Upregulated	Interacts with **YBX1**, stabilizes **EGFR** mRNA	Enhances proliferation and lapatinib resistance	Predictive of poor response to TKIs

Amplification of the 8q24 region in breast cancer may lead to an increased copy number of the PVT1 gene or the accumulation of inherited modifications in its promoter region, thereby restricting PVT1 expression [98]. The upstream promoter of PVT1 exerts a tumor-suppressive effect independent of lncRNA transcription and plays a crucial role in the tight regulation of MYC expression [99]. In breast cancer cell lines, the intragenic enhancers within the PVT1 gene body compete with the MYC and PVT1 promoters for binding. Because the PVT1 promoter interacts with the neighboring enhancers, only the PVT1 transcript is expressed when it is operation [100]. The intragenic enhancers rewire the non-functional PVT1 promoter towards the MYC promoter enhancing the oncogenic expression of MYC, thereby facilitating the proliferation of cancer cells through a topological reorganization of the 3D genome [101].

It appears that this enhancer retargeting mechanism is not unique to the PVT1-MYC combination. Because of topological changes in the genome that might strengthen the production of oncogenes, cancer cells frequently accumulate mutations in the promoters of genes. This study identified a p53-responsive region on a downstream TSS for Pvt1 that could cause the production of the Pvt1b isoform and the simultaneous suppression of Myc transcription under stress and upon p53 engagement [102]. Since the repression of Myc takes place in cis when topological rearrangements are absent and is reversed when antisense oligonucleotides that target Pvt1b are present, the scientists proposed that this mechanism is RNA-dependent [103]. Although this process in human cancers is still unclear, it suggests that lncRNA has a part in regulating important stress response pathways, including the p53-coordinated one [104-105].

Though long non-coding RNAs [lncRNAs] have grown into crucial regulators of genes, their role in a number of biological operations, including cancer, remain uncertain. A few of the primary claims and disputes pertaining to lncRNAs. Although several lncRNAs have been noticed, little is known concerning their roles in function. Maybe they serve as basic regulatory byproducts or play crucial positions of regulation in cellular processes is still up for disagreements. The means in which lncRNAs carry out their roles are still up for dispute. While some studies contend that lncRNAs interact with RNA-binding proteins and regulate transcription, others suggest that they operate as molecular the

scaffolding that lure proteins towards particular loci. Consensus is rendered more difficult by a range of methods. Although LncRNAs are frequently expressed at low levels, it might be challenging to discover and validate the way they work. This raises questions about the studies' capacity to be reproduced. Additionally, some lncRNAs express themselves differently among various tissues or cancers, which can cause confusion when interpreting results from large datasets. Whereas a large number of lncRNAs have been linked to cancer, there is ongoing contention on the clinical importance of them. The robustness and specificity of lncRNAs in clinical situations are questioned by some research, while others illustrate the potential as biomarkers or targets for therapy. Insufficiently rigorous monitoring, inconsistent outcomes, or failure to tell the difference between functional and non-functional lncRNAs are some of the explanations for why some lncRNA study are criticized. The most effective method for confirming the practical importance of lncRNAs is an ongoing subject that is constantly debate. Non-coding RNAs that are tiny as well as additional RNA species may share functional redundancy with certain lncRNAs. This overlap brings to attention how distinct lncRNAs' function are in particular circumstances.

3. Results

Challenges and Recommendation

It is not unexpected that numerous long non-coding RNAs have prevalent protein-binding domains, along with unique DNA-targeting sequences that differ between developmental stages if the complicated ontogenies of creatures and, to a lesser degree, vegetation, utilize an enormous quantity of RNAs for controlling epigenetic regulatory decisions at every phase of cell division. Discovering which lncRNAs and their modules that cooperate with proteins that affect gene regulation, and which ones exhibit target selectivity (DNA or RNA), is the hardest part. The multisubunit arrangement of many RNP compounds hampers the first; however, innovations like iCLIP422, RAP–MS423, ChIRP-MS388 and iDRiP424 deal with this issue. More difficult still is figuring out the specificity of the target given the magnitude of RNA–RNA and RNA–DNA interactions425, particular targeting only requires a brief period of nucleic acid mutual complementarity. However, novel approaches that assess RNA–chromatin and RNA–RNA interactions, such as GRID-seq426, RADICL-seq427, RIC-seq428 and RD-SPRITE353, may be competent to lend a hand. It is also necessary to characterize the components of the cytoplasmic compartments in which other lncRNAs are found. A more thorough understanding of cell and developmental biological processes as well as gene environment interactions will lead to improved insight into the functions of long non-coding RNAss along with the way they work in dynamically assemblages with other biomolecules. Understanding whether lncRNAs and RNA shifts influence cognitive flexibility, especially within the cerebral cortex, and how these lncRNA-mediated mechanisms malfunction in neurological disorders, cancer, and other disorders are instances of developing obstacles. We recommend using the generic label "lncRNA" for non-coding RNAs greater than 500 nt in absence of an accurate categorization. We suggest naming long non-coding for themselves and in relation to a noticed distinctive or work [as has been standard for protein molecules], preferred together with complete exon–intron structures and genomic coordinates, unless they are antisense to the protein-coding gene in question [in which case the wording "gene name-AS" should be used]. We advise labeling the lncRNA using the GENCODE approach if no physiological background is provided. We propose that complete transcript analysis of the isoforms and stoichiometry of mRNAs, RNA molecules called and short RNAs in lymphocytes at multiple phases of differentiation, thereby and additionally during different physiologic and illness conditions, acquiring knowledge, and situations of stress, ought to constitute a part of prospective transcript expression profiling.

Cellular-based, organoid-based, and in vivo studies utilizing techniques for restricted tissue-specific, or cell type-specific gain-of-function and loss-of-function of lncRNAs ought to complement these initiatives. In general terms, the following will be needed for recognizing and understanding the significance of lncRNAs and RNA network regulation in multicellular growth and development, cellular ecology, and disorder: The determination of how lncRNAs, amino acids, chromosome changes, and the genome cooperate to construct the nuclear domains necessary for transcription, splicing, enhancer operate and chromatin construction. A development of intracellular RNA-tracking techniques and antibodies with high sensitivity for protein–RNA complexes will be needed for this endeavor. Employing a variety of sequencing techniques, chemical probing, techniques for imaging, and superconducting microscopy of electrons to identify the positions of lncRNAs, structure–function associations, and connections. The discovery and explanation of the myriad unidentified cytoplasmic and nuclear compartments

that are ornamented with certain lncRNAs. Use machine learning to examine massive transcriptomic, proteomic, phenomics, genomic, and epigenomics, which information with the aim to discover connections between events and routes.

4. Conclusion

Future prospective and Conclusion

This review analyzes the role of LncRNA in progression in breast cancer by examining several LncRNA key characteristics. The impact of lncRNAs on cellular and tumor biology is as diverse as the molecular mechanisms through which they operate. We highlight some of the most significant recent findings, emphasizing that breast cancer remains one of the most extensively studied tumor types in this context. Although it is widely recognized that lncRNAs play a crucial role in gene regulation either globally or by fine-tuning the expression of specific target genes the complexity of their functions and biological activities presents a major challenge in lncRNA research. However, recent technological advancements, including new sequencing methodologies that go beyond short-read sequencing, offer promising opportunities to revitalize this field and drive the discovery of new foundational insights. In addition to contributing to the characterization of cancer phenotypes, lncRNAs are now also considered as valuable biomarkers of pathological states and potential therapeutic targets. Given that RNA is generally easier to target and degrade than proteins or DNA, and considering the high tissue- and cell-type specificity of lncRNA expression, they offer promising avenues for highly targeted therapeutic strategies. These features underscore the importance of investigating lncRNAs in the context of disease pathology.

Although RNAs (ncRNAs) such as H19 and XIST were identified prior to the genomic era, not fully explained and researched until the early 2000s. The development of DNA sequencing technologies, such as RNA sequencing, has made it easier to uncover the function of these lncRNAs and their involvement in various pathologies and infectious diseases. The molecular characterization of breast cancer is greatly influenced by the assessment of differential expression of lncRNAs using single-cell RNAseq and high throughput RNAseq methodologies. Several research teams are utilized these advanced tools to identify many kinds of lncRNA genes and defines them across different illnesses, including cancer. These lncRNAs have been connected to multiple signaling pathways through bioinformatics and gene enriched analysis, and this additionally highlighted the value of treatment monitoring and their diagnostic benefits. Despite growing knowledge of lncRNAs and their disease associations, their clinical application remains limited. In specific genetic subtypes of breast cancer, however, experimental and clinical data support the use of lncRNAs as predictive and prognostic biomarkers. As the clinical relevance of lncRNAs becomes clearer, their use will enhance diagnostic precision and reduce result variability in breast cancer management.

Ethical Considerations

Compliance with ethical guidelines

Not applicable

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Author's contributions

HMS conceived the study; MM designed the study design and wrote the first draft. RM performed language editing and suggested for quality improvement. HMS supervised the project and performed the final editing. HA and HMS performed literature search and collection and proofread the manuscript all authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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